

Application No. 10/817,622

Reply to Office Action

*AMENDMENTS TO THE CLAIMS*

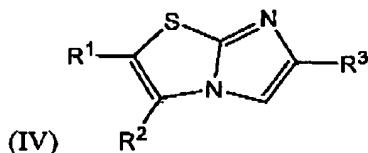
This listing of claims replaces all prior versions, and listings, of claims in the application.

1. (Currently Amended) A method of inhibiting cell death in a mammal, wherein the method comprises administering to a mammal an effective amount of a composition comprising a cell protection factor covalently linked to a bone targeting agent via a linkage that is ~~cleaved~~ cleavable under physiological conditions, whereby the cell protection factor is released from the bone targeting agent *in vivo* to inhibit cell death.

2. (Original) The method of claim 1, wherein the cell protection factor is a temporary p53 inhibitor.

3-5. (Canceled)

6. (Original) The method of claim 2, wherein the cell protection factor is a compound of Formula IV:



wherein R<sup>1</sup> and R<sup>2</sup> are taken together to form an aliphatic or aromatic carbocyclic 5- to 8-membered ring, optionally substituted with one or more straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C<sub>1</sub>-C<sub>6</sub> alkylamino, and/or C<sub>4</sub>-C<sub>14</sub> aromatic or heteroaromatic moieties, and

R<sup>3</sup> is selected from the group consisting of a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> alkoxy group, and a phenyl group, wherein the alkyl group, the alkoxy group, or the phenyl group is optionally substituted with one or more straight or branched C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino, C<sub>1</sub>-C<sub>6</sub> alkylamino, and/or C<sub>4</sub>-C<sub>14</sub> aromatic or heteroaromatic moieties.

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7. (Original) The method of claim 6, wherein  $R^1$  and  $R^2$  are taken together to form a 5- or 6-membered aliphatic carbocyclic ring optionally substituted with one or more  $C_1$ - $C_6$  alkyl groups.

8-10. (Canceled).

11. (Original) The method of claim 1, wherein the inhibited cell death is bone marrow cell death.

12. (Currently Amended) The method of claim 11, wherein the cell death to be inhibited is caused by exposure to at least one chemical or radiation.

13. (Original) The method of claim 6, wherein the inhibited cell death is bone marrow cell death.

14. (Currently Amended) The method of claim 13, wherein the cell death to be inhibited is caused by exposure to at least one chemical or radiation.

15 - 16. (Canceled).

17. (Original) The method of claim 1, wherein the mammal comprises at least one tumor.

18. (Original) The method of claim 17, wherein the mammal comprises at least one  $p53^+$  tumor.

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19. (Original) The method of claim 6, wherein the mammal comprises at least one tumor.

20. (Original) The method of claim 19, wherein the mammal comprises at least one p53<sup>+</sup> tumor.

21 - 22. (Canceled).

23. (Original) The method of claim 1, wherein the bone targeting agent is selected from the group consisting of a bisphosphonate, a hydroxybisphosphonate, a phosphonate, a phosphate, an aminomethylenephosphonic acid, and an acidic peptide.

24. (Canceled).

25. (Original) The method of claim 6, wherein the bone targeting agent is selected from the group consisting of a bisphosphonate, a hydroxybisphosphonate, a phosphonate, a phosphate, an aminomethylenephosphonic acid, and an acidic peptide.

26. (Canceled).

27. (Currently Amended) The method of claim 1, wherein the ~~linker~~ linkage is an acid-cleavable ~~linker~~ linkage.

28. (Canceled).

29. (Currently Amended) The method of claim 6, wherein the ~~linker~~ linkage is an acid-cleavable ~~linker~~ linkage.

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30. (Canceled).
31. (Currently Amended) The method of claim 27, wherein the ~~linker~~ linkage is an enol ether, ketal, imine, oxime, hydrazone, semicarbazone, acylimide, or methylene radical.
32. (Canceled).
33. (Currently Amended) The method of claim 29, wherein the ~~linker~~ linkage is an enol ether, ketal, imine, oxime, hydrazone, semicarbazone, acylimide, or methylene radical.
34. (Canceled).
35. (Currently Amended) The method of claim 1, wherein the ~~linker~~ linkage is a hydrolytically cleavable ~~linker~~ linkage.
36. (Currently Amended) The method of claim 1, wherein the ~~linker~~ linkage is ~~cleaved~~ enzymatically cleavable.
37. (Original) The method of claim 1, wherein the mammal is a human.
- 38-74. (Canceled).
75. (Previously Presented) The method of claim 7, wherein the cell protection factor is pifithrin- $\beta$ .

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76. (New) A method of inhibiting cell death in a mammal, wherein the method comprises administering to a mammal an effective amount of a composition comprising a cell protection factor covalently linked to a bone targeting agent via a linkage that is cleavable under physiological conditions, whereby the cell protection factor is released from the bone targeting agent *in vivo* to inhibit cell death, wherein the cell protection factor is a temporary inhibitor of a tumor suppressor gene, the bone targeting agent is a ligand that binds hydroxyapatite, and the linkage is an organic moiety comprising a nucleophilic or electrophilic reacting group which allows covalent linking to the bone targeting agent.

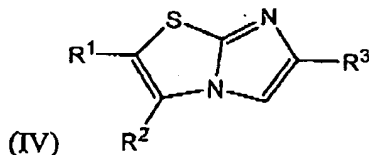
77. (New) A method of inhibiting cell death in a mammal, wherein the method comprises administering to a mammal an effective amount of a composition comprising a cell protection factor covalently linked to a bone targeting agent via a linkage that is cleavable under physiological conditions, whereby the cell protection factor is released from the bone targeting agent *in vivo* to inhibit cell death, wherein:

the cell protection factor is a temporary p53 inhibitor;

the bone targeting agent is selected from the group consisting of a bisphosphonate, a hydroxybisphosphonate, a phosphonate, a phosphate, an aminomethylenephosphonic acid, and an acidic peptide; and

the linkage is an enol ether, ketal, imine, oxime, hydrazone, semicarbazone, acylimide, or methylene radical.

78. (New) The method of claim 77, wherein the cell protection factor is a compound of Formula IV:



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wherein  $R^1$  and  $R^2$  are taken together to form an aliphatic or aromatic carbocyclic 5- to 8-membered ring, optionally substituted with one or more straight or branched  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino,  $C_1$ - $C_6$  alkylamino, and/or  $C_4$ - $C_{14}$  aromatic or heteroaromatic moieties, and

$R^3$  is selected from the group consisting of a  $C_1$ - $C_6$  alkyl group, a  $C_1$ - $C_6$  alkoxy group, and a phenyl group, wherein the alkyl group, the alkoxy group, or the phenyl group is optionally substituted with one or more straight or branched  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, hydroxy, fluoro, chloro, bromo, nitro, amino,  $C_1$ - $C_6$  alkylamino, and/or  $C_4$ - $C_{14}$  aromatic or heteroaromatic moieties.